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On the changes in the walls of the small splenic arteries.

by G. Matsuno.

Virchow's Archives, 240: 69-80 (1923).

In the question of the connection between general high blood pressure, hypertonia, and changes in the small arteries has been raised, the arterioles of the kidney were the first to be subjected to extensive study, followed by those of other organs such as the pancreas and the liver. The spleen has also been included in the scope of such investigations, but some authors, e.g. Fahr and Herxheimer, have pointed out that the vascular alterations of this organ are to be evaluated differently from the arterioles, for example, of the kidneys. Herxheimer, particularly, has treated this question by means of extensive material and has concluded that 53% of 1,140 spleens examined indiscriminately revealed a change of the small vessels, the small trabecular arteries, penicillus arteries and the smallest precapillary arteries. This change consists of a thickening and hyaline expansion of the inner vascular wall layers in the entire circumference of the vessel or only in a portion of its dimension; fatty degeneration has developed to a low degree only. The elastic fibers fail to show important changes. According to Herxheimer, this hyaline degeneration of the wall of the small splenic vessels increases in frequency and severity with advancing age. It is rarely found in children under 10 years of age and then only sparsely, while it is found in one half of all cases between the ages of 10 and 40, often with advanced development, and in 2/3 to 3/4 of all cases aged 40-70, quite frequently with a high degree of development. A noteworthy influence of the diseases affecting the examined material on the condition of the small splenic vessels generally could not be established.

On the basis of this research, the evaluation of the changes of the small splenic arteries described in relation to the explanation of pathological conditions such as hypertonia, becomes highly questionable in view of their high incidence. Recent findings of Eppinger dealing with the small splenic vessels in hemolytic icterus and especially with pernicious anemia, therefore seem the more noteworthy. He found conspicuously thickened walls in the central arteries with multiple shredding of the elastica, particularly in the latter disease. New tissue is deposited between the elastica and the intima, which frequently is oddly opaque, stains an intense red like hyaline with eosin, and gives a yellow to Bordeaux red reaction to Mallory's stain. These hyaline masses are contained in the intima now in spots, now throughout the entire vascular circumference. Eppinger stresses that he has found these hyaline deposits in only 3/4 of the examined cases, but that changes were invariably demostrable in the small splenic vessels, and that he claims to recognize in them "a typical alteration of the pernicious spleen." In this respect a great similarity exists between the findings in pernicious anemia and in hemolytic icterus. In both diseases "the damaged vessels point to

typical circulatory conditions," which may be followed by the penetration of erythrocytes into the splenic pulpa. Concerning the hyaline degeneration of the small splenic vessels found by Herxheimer, Oppinger states that he has seen similar conditions, but thinks "that these changes, at least quantitatively, have no bearing on those described by us in connection with pernicious spleen."

These data recently prompted us to subject the small splenic vessels to a histological examination, with particular stress on the question whether the type and degree of alteration could actually be related to certain pathological processes. For this purpose the customary sectional material was resorted to without selection, so that persons of various ages and with the most varied disease processes were examined. Since, as the following elucidations will show, the findings repeated themselves with tolerable regularity, we believed ourselves justified in dispensing with a further expansion of the investigation and will report below on a material encompassing 323 cases.

Concerning the classification of the splenic arteries we followed the generally accepted nomenclature (cf. Sobotta), according to which the arteries situated in the trabeculae become narrower in their onward course and receive a sheath of typical lymphatic tissue (at a circumference of 0.15 mm). This sheath becomes thicker in places, particularly at the forks of the small arteries, and forms the Malpighian bodies in which the vessels ("central arteries") are always located eccentrically. Frequently 2-3 such central arteries are situated in one follicle. As the arteries leave the splenic nodules and reach the pulpa with a diameter of 0.05 mm, they fork out into a large number of small precapillary branches known as penicillus arteries. These are 15-30 microns thick and ordinarily have no lymphatic sheath. Before they change to the capillaries proper, their walls undergo a repeated thickening which is connective tissual - fibrous and has given the basis for the designation of these branches as enveloped arteries. In the trabecular and larger central arteries the differentiation of individual wall layers, the intima, elastica interna and usually the media, may be made in the same manner as that of the other arteries; as a rule the wall of the penicillus arteries reveals only a few elastic fibers. They seldom form a closed ring circling the whole lumen. Muscle fibers are often recognizable in the wall of the penicillus arteries, but by no means in all cases.

The histological examination of these vessels yielded normal results in 79 cases = 24.5% of our material, and this, as should be noted, primarily in younger persons. In these cases the vessels have a lumen corresponding to their circumference, their intima is very delicate and thin, is formed in the central arteries almost solely of endothelium, the elastica consists of a wide, uniform, easily stained belt, especially in the trabecular arteries, but also in the larger central arteries; the media has an appropriate thickness, its muscle bundles are distinctly shown by the Gieson stain and contrast clearly against the inner and outer wall layers. In the remaining 244 cases = 75.5% of the examined material, histological observation of the small vessels disclosed changes

in their walls, affecting all vessels (trabecular, central and penicillus arteries) equally in 128 cases, the follicular and penicillus arteries only in 100 cases, whereas the trabecular arteries did not show essential alterations. Isolated involvement of the trabecular or follicular or penicillus arteries was demonstrated in only 4 cases each, and 4 cases showed simultaneous affection of the trabecular and follicular arteries without involvement of the penicillus arteries.

In the overwhelming majority of the cases considered here, the follicular and penicillus arteries revealed a variable, often quite considerable thickening of their wall, causing the lumen to be reduced, frequently to a narrow slit, or (especially in the penicillus arteries) even to be closed entirely (cf. Fig. 1, spleen of a 22-year-old man, and Fig. 2, spleen of a 67-year-old woman). Stained with hemalum-eosin, the vascular wall in such cases usually shows a thick, homogeneous, often hyaline belt, uniformly stained red with eosin, within the borders of which a delineation of intima and media becomes impossible. Isolated nuclei of endothelial cells may still be recognized near the inner limit of the lumen and on the periphery of the vascular wall, while usually absent from within the homogeneous belt. In the larger central arteries and the trabecular arteries the widening of the intima usually is not as extensive as in the smaller vessels, relative to the vascular circumference, nor does the homogenization of the walls progress that far, so that the thickened intima may be delineated from the relatively narrower media. In the majority of cases the elastic fibers show few changes in the smaller vessels, even with considerable widening of the wall (Fig. 1). Frequently the elastic fibers of the penicillus arteries are not distinctly seen, the outer periphery of the more or less thickened vessel often shows 1 or 2 delicate, circularly oriented fibers that normally do not form a closed belt. The follicular arteries similarly fail to reveal important changes of the elastic fibers, at times even in cases showing considerable thickening and homogenization of the wall. In other cases of this type (Fig. 2) the elastica is again split into two or three lamellae, at times small, delicate, irregularly arranged fibers are seen which cross the lamellae. The trabecular arteries show this type of alteration far more frequently; the cleavage of the elastica into several lamellae was a frequent observation among our material; newly formed elastic fibers in the thickened intima were also by no means rare. Mallory's stain was also used in more detailed studies of the changes in the vascular wall. In those cases where the vascular wall was unimpaired, this stain revealed a structure of delicate, blue-stained lamellae; the cases with thickened vessels were different. A small portion of the latter also showed a blue Mallory reaction in the wall, but it consisted of thicker, cruder trabeculae; usually the intima appeared to be stained orange or a vivid red, fluctuating in range; at times only isolated orange-yellow or red deposits were seen in the wall, then again the thickened intima had been transformed into a vividly red belt, either completely or in major proportions (Fig. 3). These changes had usually developed similarly in all arteries (penicillus, follicular and trabecular arteries), but frequently the individual arteries were different in that the wall of the small arteries had stained red to a varying degree, whereas that of the larger

arteries was blue. The elastica of the latter frequently stained yellow or yellowish-red with Mallory, at times there were yellow or red clods within the media. Mallory's stain was used in 230 out of 244 cases with thickened vascular walls. In 41 cases orange or red stains were absent from the wall, in 80 cases there were red or orange clods of minor scope deposited in the vascular wall; in 109 cases, primarily of advanced age (cf. later), this alteration was developed to a high degree.

In a small portion of the material (49 cases) the frozen sections were stained with Sudan. In 27 cases the vascular wall was free of fat, in 7 cases there were isolated fatty droplets, in 15 cases somewhat more fat within the vascular wall, primarily in the intima.

The degree and extent of the changes described showed considerable fluctuations, not only in the vessels of different cases, but also in the vessels of the same case; all vessels of a spleen were not always altered in the same manner. In the penicillus arteries as well as in the follicular arteries we noted that individual vessels were quite considerably thickened, their lumens were almost entirely closed, while others had a relatively thinner wall and a wider lumen; the same is true relative to the reaction to Mallory's stain. Frequently one part of the vascular wall appeared to be constructed of thin, blue lamellae, while other parts showed vividly red deposits in their wall.

If we scan the vascular alterations revealed by our material and briefly outlined herein, the result is a complete agreement with Herxheimer's findings. We do not attach much significance to the fact that this author found changes in the small splenic vessels of only 53% of the cases, while we noted them in 75.5% of our material. Ignoring the fact that the investigations were conducted at different locations and at different times, the evaluation of low-grade changes as such is rather subjective, and numerical differences may easily result from this circumstance. Herxheimer himself writes that he counted only those cases that disclosed changes in a large number of vessels, his figure would have been considerably larger otherwise. It is far more important that we observed precisely the same changes qualitatively as those described by Herxheimer, and that we came to the same conclusions in other respects, as will be shown subsequently.

The summarized description of our findings indicates that many cases revealed exactly the same changes as those described by Eppinger as typical alterations in pernicious anemia. His elucidations and illustrations of vascular changes coincide in the minutest details with changes demonstrated by us in many cases. It is necessary, therefore, to investigate whether a connection exists between the described alterations of the small splenic vessels and certain pathological processes.

In this respect, initial attention must be devoted to a tabulation of the material according to the age of the individuals involved.

Age	All vessels normal	Trabecular arteries changed	Follicular arteries changed	Penicillus arteries changed	Trabecular and follicular art. changed	Follicular and penicillus art. changed	All vessels changed	Total
0-10	12=85.7%	-	-	-	-	2=14.3%	-	14
11-20	23=69.7%	-	-	-	-	10=30.3%	-	33
21-30	19=51.3%	1	-	1	-	14=37.8%	2=5.4%	37
31-40	11=30.5%	-	-	1	-	16=44.5%	8=22%	36
41-50	5=11.6%	1	3	-	1	16=37.2%	17=39.5%	43
51-60	4= 6.8%	-	-	2	2	18=30.5%	33=55.8%	59
61-70	4= 5.9%	1	1	-	-	16=23.9%	45=67.2%	67
71-80	1= 4 %	1	-	-	1	8=32 %	14=56%	25
over 80	-	-	-	-	-	-	9=100%	9
Total	79	4	4	4	4	100	128	323

This table indicates that the splenic vessels almost invariably remain unchanged in childhood; alterations of the small vessels were found in only 2 cases. It must be noted that examination of the spleen of 14 fetuses of different age never revealed changes in the small splenic vessels. The table further shows that alterations of the splenic arteries occur relatively early at a youthful age, becoming more frequent with advancing age. The percentage of normal vessels decreases rapidly, while the number of cases with altered vessels increased correspondingly. Initially, only relatively low-grade changes of the small penicillus and follicular arteries are involved. At age 20-30 years the number of cases with normal and with altered vessels are approximately equal; later the figure representing changed vessels rapidly becomes larger, among these a growing share of cases in which all splenic arteries are changed, thus deserving the designation of high-grade involvement. The hyaline transformation of the vascular wall has a parallel course, as shown by the following table representing the reaction of thickened vessels to Mallory's stain.

Age	Widening of the vascular wall without	/ with moderate	/ with considerable hyaline transformation	Total of examined cases
0-10	-	2	-	10
11-20	2= 8.3%	7=29 %	-	24
21-30	7=21.9%	10=31.2%	2= 6.2%	32
31-40	8=22.2%	16=44.5%	4=11 %	36
41-50	9=22 %	15=36.5%	15=36.6%	41
51-60	10=20 %	12=24 %	25=50 %	50
61-70	5= 8.9%	11=19.3%	39=68.4%	57
71-80	-	7=28 %	17=68 %	25
over 80	-	-	7	7

It is shown that the widening of the vascular wall in youth generally is attributable to an increase in intimal connective tissue without or with moderate hyaline transformation; the latter gains in scope, so that the cases with advanced hyaline transformation are in the vast majority after about the 50th year. Fig. 4 shows that the latter may already occur in youth, as indicated by the splenic arteries of a 22-year-old man who died of tuberculous meningitis. The changes show extensive similarity with those depicted in Fig. 3; here the spleen of a 67-year-old woman is involved who suffered from general atherosclerosis.

In order to establish whether a connection between the described vascular changes and the disease of the individual really exists, we arranged the whole material according to the basic diseases indicated in the individual cases. In this connection those processes that made an effect on the splenic vessels probable, judging by other pathologic-anatomical experiences, were considered separately, while other diseases were consolidated in one group. Still, the distribution on the individual age groups had to be considered simultaneously in this tabulation, as indicated by the present considerations, since a certain form of disease could easily simulate an influence on the condition of the splenic vessels, whereas the result really depended on the circumstance that a large number of older or younger individuals had been examined coincidentally. Giving due consideration to these aspects, the following table results. (The table is appended).

The compilation reveals that the type of disease surely has no important effect on the changes of the small splenic vessels. In certain diseases, e.g. cardiac abnormalities or tuberculosis, it really appears as if the splenic vessels had undergone changes earlier or more frequently, but our material was too inadequate and the differences found too small to permit a positive conclusion. It is noteworthy that cases with arteriosclerosis and syphilitic aortitis almost invariably had altered small splenic vessels; however, most of the individuals involved had reached an advanced age in which the changes in question are usually present in the same frequency. The cases of pernicious anemia were similar. They showed, with one exception, altered splenic vessels, but these were almost invariably cases of advanced age. We are thus able to confirm Eppinger's findings in this respect that the indicated changes of the small splenic vessels are found almost regularly in pernicious anemia, even if not without exception; but we must stress, in contrast to Eppinger, that these changes differ neither qualitatively nor quantitatively from those found quite frequently in the spleen, and that these changes therefore do not represent a typical symptom of the spleen in pernicious anemia. In this respect we were again able to confirm Herxheimer's observations. He, too, noted an increase in intensity and frequency of changes in the splenic vessels proportional to age, without being able to demonstrate a correlation with the type of disease afflicting the individuals. Herxheimer found a greater incidence and higher grades of alteration of the small and smallest splenic vessels only in arteriosclerosis, confirmed by our own findings. The extent to which our results coincide with those of Tsunoda cannot be judged owing to the limited data.

Concerning the type of changes observed, these evidently are not consistent in nature. In part of the cases there is only a widening of the intima without changes in the elastic fibers and without regressive alterations (hyaline transformation, reaction to Mallory's stain), while another part gives evidence of rather severe changes in the elastica and quite extensive hyaline transformation of the vascular wall. Fatty degeneration seems to occur to a relatively moderate extent, if the small number of relevant observations permits such a conclusion. The changes discovered must therefore be evaluated separately. In part of the cases a thickening, hyperplasia of the intima is involved, angiofibrosis, another part reveals alterations which doubtless must be classed with atherosclerosis. The fact that thickening of the small arteries, angiofibrosis, occurs so early in the spleen, and almost regularly with advancing age, and that frequently atherosclerosis is also present, and this often in cases without general atherosclerosis, must be ascribed to local conditions. The thought suggests itself that the small splenic arteries are subjected to repeated distension due to considerable functional utilization and frequent effects of impairment, only in part equalized by connective tissue proliferation of the intima. Thus the early occurrence of angiofibrosis of the small splenic arteries, found quite often and present almost regularly in advanced age, might also be interpreted as a compensatory process similar to intimal proliferation or some forms of endarteritis obliterans in other arteries that are subject to particularly active functional utilization and also show early and frequent intimal thickening of varying degree. The same considerations ought to explain the circumstance that the small splenic arteries often give evidence of atherosclerotic changes, even in cases where the remaining arteries are not diseased. With reference to the interpretation of the alterations found in the small splenic arteries, we therefore deviate somewhat from Herxheimer, who does not classify them with ordinary atherosclerosis, although he also describes them as "a manifestation of functional detrition or adaptation."

→ The segmental splenic

At any rate, it may be considered as established that intimal thickening leading to narrowing of the vascular lumen as well as the hyaline transformation of the vascular wall are found early in the small splenic arteries, an observation that increases in frequency with advancing age and to which a pathogenetic significance for certain diseases cannot be assigned. ( ) ←

Illustrations.

Fig. 1. Spleen of a 22-year-old man.
Fig. 2. Spleen of a 67-year-old woman.
Fig. 3. Spleen of a 67-year-old woman.
Fig. 4. Spleen of a 22-year-old man.

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Age	Cardiac abnormalities normal	Cardiac abnormalities changed vessels	Arterio-sclerosis K	Arterio-sclerosis C	Syphilitic aortitis K	Syphilitic aortitis C	Tuberculosis normal	Tuberculosis changed vessels	Malignant tumors normal	Malignant tumors changed vessels	Pernicious anemia K	Pernicious anemia C	Other diseases normal	Other diseases changed vessels
0-10	-	-	-	-	-	-	1	-	-	-	-	-	11=85%	2=25%
11-20	-	-	-	-	-	-	2=40%	3=60%	-	-	-	-	21=75%	7=35%
21-30	3=50%	3=50%	-	-	-	-	1=17%	5=83%	2=67%	1=33%	-	-	13=59%	9=41%
31-40	1=14%	6=86%	-	2	-	2	2=50%	2=50%	-	1	-	-	8=40%	12=60%
41-50	-	4=100%	-	2	-	4	-	3	2=18%	9=82%	1	3	2=13.3%	13=86.7%
51-60	-	6=100%	1	12	-	5	-	5	2=15%	11=85%	-	5	1=8.3%	11=91.7%
61-70	2	7=80%	-	13	-	5	-	5	1	17	-	2	1=7%	14=93%
71-80	1	4=75%	-	7	-	-	-	3	-	4	-	-	-	6
over 80	-	2=100%	-	4	-	-	-	1	-	2	-	-	-	-
	7	32	1	40	-	16	6	27	7	45	1	10	57	74

Total: 323